UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Offic
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/589,589	06/08/00	HIGH	K 018743/02763

ROBERT M. BEDGOOD PH.D
PILLSBURY WINTHROP LLP
50 FREMONT STREET
SAN FRANCISCO CA 94105

HM22/1108

EXAMINER	
WHITEMAN, B	
ART UNIT	**PAPER NUMBER**
1633	12

DATE MAILED: 11/08/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/589,589	HIGH ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) *11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3,5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Non-Final Rejection

Acknowledgement to priority under 35 U.S.C. 119 (e) to provisional application 60/138,066 filed on 8 June 1999.

Information Disclosure Statement

The information disclosure statement filed on 27 September 2000 does not fully comply with the requirements of 37 CFR 1.98 because: applicant does not properly cite the journal article(s) listed on the 1449. The title of each journal article(s) is missing.

Applicant should include a new 1449 properly citing the journal articles with response to this office action. Failure to comply with this notice will result in the above mentioned information disclosure statement being placed in the application file with the non-complying information **not** being considered. See 37 CFR 1.97(i).

Applicant's election of species in Paper No. 11 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claim 11 and non-elects species of claims 4 and 9 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected embodiment, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 11.

Claims 1-10 and 12, to which the following grounds of rejection are applicable, pending examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10 and 12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) A method of inhibiting the formation of inhibitory antibodies in a mammal undergoing gene therapy, said method comprising administering to said mammal an immunosuppressive agent in conjunction with gene therapy; 2) The method of 1, wherein said gene therapy is performed by administering either an adeno-associated virus vector (AAV) or an adenovirus vector to said mammal, wherein said vector comprises a nucleic acid encoding an allogenic Factor IX; wherein said immunosuppressive agent is cyclophosphamide and does not reasonably provide enablement for the rest of the disclosure. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The field of the invention lies in preventing the formation of antibodies in a mammal undergoing gene therapy, wherein said method comprises administering to said mammal an immunosuppressive agent in conjunction with said gene therapy. Specifically, the claimed invention encompasses preventing inhibitory antibodies in mammal undergoing gene therapy for factor IX, said method comprising administering to said mammal cyclophosphamide in conjunction with said gene therapy.

The state of the art for gene therapy as exemplified by Rubanyi (Molecular Aspect of Medicine, Vol. 22, 2001, pages 113-142) teaches that:

> The most promising areas for gene therapy today are hemophilias and cardiovascular diseases. This is based on the relative ease of access of blood vessels for gene therapy, and also because existing gene delivery technologies may be sufficient to achieve effective therapeutic benefits for some of these indication (transient expression in some but not all affected cells is required to achieve a therapeutic effect at a relatively low does of vector) (abstract). For other diseases (including cancer) further development in gene delivery vectors and gene expression systems will be required. It is important to note, that there will not be a universal vector and each clinical indication may require a specific set of technical hurdles to overcome. These will include modification of viral vectors, engineering of non-viral vectors by mimicking the beneficial properties of viruses, cell-based gene delivery technologies, and development of innovative gene expression regulation systems (abstract).

Furthermore, Anderson et al., *Nature*, Vol. 392, pp. 25-30, April 1998, displays major consideration for any gene transfer or any DNA therapy protocol involve issues that include:

1) The type of vector and amount of DNA constructs to be administered,

2) The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;

3) The trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and

4) What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method (Anderson, *Nature*, Vol. 392, pp. 25-30, April 1998).

In addition, all of these issues differ dramatically based on the specific vector used, the route of administration, the animal being treated, therapeutically effective amount of the DNA, and the disease being treated.

Anderson teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (pp. 25-30).

Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack the basis understanding of how vectors should be constructed what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). Furthermore, Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target

tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2).

In further support of Rubanyi about the predictability for treating hemophilia in a mammal is exemplified by High et al (Applicants' IDS, US Patent No. 6,093,392), High teaches that one viral vector, adenovirus, has been used to effect expression of high levels of canine factor IX in immunodeficient/immunocompetent mice when the virus is administered in conjunction with immunosuppressive agent (column 1, lines 36-40). High uses a recombinant AAV vector comprising of factor IX (F.IX) to treat hemophilia in a mammal. Also, retroviral vectors have also been used experimentally a model for treatment for hemophilia B. However, levels of expression FIX from these vectors are reported to be too low to be of therapeutic value (column 1, lines 59-63). Plasmid DNA which has been injected into mouse muscle has been shown to direct expression of erythopoietin (Epo), but this method of gene therapy is not efficient for the expression of a gene product such as F.IX which is needed at relatively high levels in the circulation (compared with Epo) to achieve a therapeutic effect (column 1, lines 64-column 2 line 4).

The specification teaches a method for inhibiting the formation of inhibitory antibodies in a murine knockout model of hemophilia B undergoing gene therapy treatment, said method comprising administering to said mouse a recombinant AAV vector comprising murine factor IX (mFIX) in conjunction with anti-CD40L, cyclosporin A, or cyclophosphamide (pages 13-16). The results display that mice

injected with AAV mFIX make antibodies, which are inhibitory to the transgene product (page 15). Also, the results show that transgene expression may be increased with using an immunosuppressive agent in conjunction with delivering AAV comprising mFIX to the mice (pages 14-16).

With respect to claims 1-10 and 12 that encompass a method of preventing the formation of inhibitory antibodies in a mammal undergoing gene therapy, said method comprising administering to said mammal an immunosuppressive agent in conjunction with said gene therapy, the specification and the state of the art fail to provide sufficient guidance for one skilled in the art to use the method for preventing the formation of inhibitory antibodies in any mammal undergoing gene therapy. The working example in the disclosure displays that allogenic transgene expression maybe increased with using an immunosuppressive agent in conjunction with AAV in mice. However, in view of the unpredictability of preventing the formation of inhibitory antibodies in any mammal undergoing gene therapy, the as-filed specification fails to reasonably extrapolate from the working example to a method of preventing the formation of inhibitory antibodies in any mammal undergoing gene therapy in conjunction with any immunosuppressive agent. The state of the art for using immunosuppressive agents to prevent neutralizing antibodies against a transgene product as exemplified by Potter et al., Ann NY Acad Sci, Vol. 875, pages 159-174, 1999, Potter teaches that:

> The response of a recipient to various immunosuppressive agents can be classified into three categories. The first category, shown by treatment with

> CTLA4-Ig or interleukin-12, was similar to the untreated controls, no suppression of anti-hGH antibodies and no significant improvement in delivery of hGH. The second category of response observed in four treatment protocols (cyclophosphamide, FK506, anti-gp-39, and interferon-γ), was suppression of antibodies but no improvement in sustaining delivery of transgene product. It is clear that while these treatments are more effective in antibody suppression than CTLA4-Ig and IL-12, they were unable to exert sufficient suppression of the humoral response to permit a sustained level of circulating recombinant hGH produced by the encapsulated cells. The last category of response was seen in the group of mice receiving anti-CD4; strong antibody suppression and the most sustained hormone delivery. See pages 171-172.

In view of the state of the art and the as-filed specification, it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from inhibiting the formation of inhibitory antibodies in a mammal undergoing gene therapy in conjunction with an immunosuppressive agent to a method of preventing the formation of inhibitory antibodies in a mammal undergoing gene therapy in conjunction with an immunosuppressive agent. Also, one skilled in the art could not reasonably extrapolate from inhibiting the formation of inhibitory antibodies in mice to preventing the formation of inhibitory antibodies in any mammal undergoing gene therapy without an undue amount of experimentation. Furthermore, in view of an immune response to foreign proteins and using a transgene from one species (e.g.

murine factor IX) in another species (e.g. human, dog, etc.) for treating a genetic defect, it would take one skilled in the an undue amount of experimentation to determine in a representative number of species, if murine Factor IX could use for treating hemophilia in other species (e.g. human, dog, etc.) without observing either inhibitory antibodies to the transgene (e.g. murine Factor IX) or a therapeutic treatment. Thus, the claims are not enabled for a method of preventing the formation of inhibitory antibodies in a mammal undergoing gene therapy in conjunction with gene therapy.

In view of the In re Wands Factors, claim 3 is not enabled by the specification, which provides sufficient guidance for one skilled in the art to make and use a method of inhibiting antibodies in a mammal undergoing gene therapy for hemophilia, wherein the method comprises administering to said mammal an immunosuppressive agent in conjunction with said gene therapy and the transgene is allogenic to said mammal. One skilled in the art of gene therapy would interpret that the breadth of the claim encompasses complete correction of a genetic defect. However, in view of the breadth of the claims, the specification does not provide sufficient guidance for one skilled in the art to make and use the method described above for correcting any genetic defect (e.g. complete correction) and defects that require precise gene regulation unlike treating a mammal with a genetic disorder that does not require precise gene regulation. In view of the doubts expressed above by Anderson, Rubanyi, and Verma, the specification and prior art at the time the application was filed, the as-filed specification fails to provide sufficient guidance for

one skilled in the art to reasonably extrapolate from using gene therapy for treating the defect hemophilia in a mammal, using an allogenic factor IX, in conjunction with an immunosuppressive agent to correcting a genetic defect (complete correction of the disorder) in any mammal. Furthermore, Rubanyi teaches:

> That some applications of gene therapy require no precise gene expression regulation because they involve proteins with large therapeutic windows (such as adenosine deaminase, CFTR, and coagulation factors VIII and IX). These applications, however, represent only a small part of the clinical potential for gene therapy. Most therapeutic proteins have limited therapeutic windows, both in terms of their level and their duration of action for effective protein delivery, control over the level and duration of gene expression (page 124).

Thus in view of the In Re Wands Factors, listed above, the quantity of experimentation required to determine the delivery route of a nucleic and what amount of nucleic is required to treat a genetic disorder that requires precise regulation of gene expression, the direction provided by the as-filed specification encompasses using gene therapy to treat hemophilia, the working examples encompass treating hemophilia in a knock-out mouse model of factor IX in conjunction with cyclophosphamide, the state of the gene therapy was considered predictable when trying to treating a genetic disorder (e.g. hemophilia B) that does not require precise gene expression, the relative skill of those in the art, and the breadth of the claims; the as-filed specification fails to provide sufficient guidance for how to correct any genetic defect (complete correction) in any mammal.

At best the disclosure is enabled for: 1) A method of inhibiting the formation of inhibitory antibodies in a mammal undergoing gene therapy, said method comprising administering to said mammal an immunosuppressive agent in conjunction with gene therapy; 2) The method of 1, wherein said gene therapy is performed by administering either an adeno-associated virus vector (AAV) or an adenovirus vector to said mammal, wherein said vector comprises a nucleic acid encoding an allogenic Factor IX; wherein said immunosuppressive agent is cyclophosphamide.

In conclusion, the as-filed specification and claims coupled with the state of the art at the time the invention was made only provide sufficient guidance and/or evidence to reasonably enable 1-2 listed above. Given that gene therapy wherein any carrier is employed to correct a disease or a medical condition in any mammal was unpredictable at the time the application was filed, and given the lack of sufficient guidance as to a gene therapy effect produced by any gene delivery vector cited in the claims other than treating a mammal with a genetic defect that does not require precise gene expression, one skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the applicants' disclosure and the unpredictability of gene therapy.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 4 and 6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 recites the limitation "protein" on page 17. There is insufficient antecedent basis for this limitation in the claim. Claim 4 states, "The method of claim 3, wherein said protein is selected....". Claim 3 does not recite protein, but claim 3 does recite nucleic acid.

Claim 6 recites the limitation "human" on page 17. There is insufficient antecedent basis for this limitation in the claim. Claim 6 states, "The method of claim 1, wherein said gene therapy is performed by administering a viral vector to said mammal, wherein said viral vector comprises a nucleic acid to be delivered to said human." Claim 1 does not recite human, but claim 1 does recite mammal.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1, 2, 3, 4, 5, 9, 10, and 12 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Tengborn et al (Haemophilia, Vol. 4, Jan 1998, pages 56-59). Tengborn teaches that a high dose regimen with factor IX in combination with cyclophosphamide and gammaglobulin administered intravenously according to the Malmo model has been used for the induction of immune tolerance in haemophilia B complicated inhibitor formation with a success rate of 85% (6 out of 7 cases) in haemophilia B (page 56).

Claims 1-6, 9-10, and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Trapnell et al (WO 97/39776). Trapnell teaches a method of gene therapy treatment in host, comprising the steps of (a) administering to a host (i) an adenoviral vector including at least one DNA sequence encoding a therapeutic agent; (ii) deoxyspergualin, and (iii) cyclophosphamide (page 56).

Claims 1-10 and 12 are rejected under 35 U.S.C. 102(e) as being anticipated by High et al (Applicants IDS, US Patent No. 6,093,392) in further view of Smith et al. (Gene Therapy, vol. 3, 1996, pages 496-502). High claims a method of treating hemophilia in a mammal comprising: a) providing a recombinant AAV comprising a nucleic acid encoding Factor IX; and administering an amount of said AAV to a mammal wherein said factor IX is expressed at levels having a therapeutic effect on said mammal (column 29, claim 1. In addition, High teaches that adenoviral vectors are well known in gene therapy and have been used to effect expression of high levels of canine factor IX in immunodeficient/immunocompetent mice when the virus is administered in conjunction with immunosuppressive agent (column 1, lines 36-40). Smith teaches that multiple intravenous administration of adenovirus vectors resulting transgene expression can be accomplished in immune competent animals treated with a short course of immunosuppression at the time of vector delivery (pg. 499, 1st paragraph under discussion). More specifically, Smith demonstrates that the humoral immune response to a systemically administered adenovirus vector is dose dependent and can be modulated by a brief treatment with the immunosuppressive agent cyclophosphamide at the time of the initial treatment. This strategy permits effective multiple repeat doses of a vector encoding a therapeutic gene such as Factor IX (pg. 496). This demonstrates that employing the immunosuppressive agent,

cyclophosphamide, in conjunction with a method of gene therapy for treating hemophilia to increase the efficiency of gene transfer and the expression of the nucleic acid encoding the protein Factor IX in a mammal was anticipated by High in view of Smith. Absence evidence to the contrary, High in view Smith use the same method and materials as contemplated by the as-filed specification and the method would have resulted in intrinsically inhibiting the formation of inhibitory antibodies specifically binding with the transgene being expressed in said mammal.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ms. Tracey Johnson whose telephone number is (703) 305-2982. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark can be reached at (703) 305-4051.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-2742.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
1633

DAVE T. NGUYEN
PRIMARY EXAMINER

11/02/01